Review

Cancer Therapy with Phytochemicals: Present and Future Perspectives

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Recently, a wide range of food-derived phytochemical compounds and their synthetic derivatives have been proposed for cancer treatment. Unfortunately, data available in related literature focus on the anti-cancer properties of compounds derived from edible plants, while very little is known about those derived from non-edible plants. And thus, the underlying mechanisms of their anti-cancer effects are yet to be elucidated. This review collates the available data on the anti-cancer activities of six phytochemical-derived compounds from edible and non-edible plants, i.e. rottlerin, berbamine, sparstolonin B, sulforaphane, plumbagin and 6-shogaol. These compounds are used as bioactive markers for cytotoxicity against tumors. As such, understanding their mode of action will provide the rationale for the combination strategies of these compounds with other drugs in the battle against cancer.

It has been estimated that 25%-48% of current approved therapies by the Food and Drug Administration (FDA) are derived from plants[1-3]. Phytochemicals in fact are non-nutritive compounds derived from plants. These compounds have unique properties which enable them to act as potent anti-inflammatory and anti-cancer agents[4]. Fruits, vegetables and herbs are the main source for these phytochemical-derived compounds. Surprisingly, more than 10,000 phytochemicals have been identified and used in cancer treatment due to their anti-cancer properties[5]. Additionally, phytochemicals could synergistically increase the efficiency of anti-cancer drugs and reduce their toxic effects[6-7]. The aim of this review is to discuss the mechanisms underlying the cellular and molecular effects of six compounds via various signaling pathways essential for cancer cell survival.

ROTTLERIN

Rottlerin is a natural plant polyphenol compound derived from the kamala tree (*Mallotus philippinensis*). Rottlerin possesses a cytotoxic effect against a wide spectrum of tumors and cancer cells including those which are apoptotic competent and apoptotic resistant[8-9]. Despite its well documented anti-cancer properties, yet the exact mechanisms of rottlerin's anti-cancer effects are not known. Table 1 provides a summary for the molecular mechanisms underlying rottlerin's anti-proliferative activities against cancer cells.

Mechanisms of Rottlerin-induced Cancer Cell Death

Apoptotic pathways Rottlerin could induce intrinsic apoptosis, characterized by a dissipation of mitochondrial ΔΨm, and extrinsic apoptosis accompanied with a concomitant induction of TRAIL receptors, DR4 and DR5, with caspase-8 activation[10]. Rottlerin could also interact directly with proteins of the Bcl-2 family of the mitochondria and stimulates cytochrome c release[11]. The inhibition of PI3K/Akt/mTOR pathway and the activation of caspase cascade are also potential mechanisms for apoptosis induced by rottlerin[12]. Another potential mechanism for rottlerin's apoptotic effect is its ability to impair DNA repair machinery via initiating of γH2AX, a hall marker of DNA damage response[13]. Upon PKCδ inhibition, the stress-responsive JNK pathway activates and thus promotes the activation of H2AX accompanies with the induction of caspase-dependent apoptosis[14].

Inhibition of Nuclear Factor-κB (NF-κB) The transcription factor NF-κB transcription factor is constitutively activated and plays a major role in the development and progression of a wide spectrum of cancer cells[15]. The up regulation of IκB kinase-NF-κB signaling pathway is important for promoting treatment resistance through induction of survival genes, and preventing host toxicity in cancer chemotherapy[16]. Rottlerin increases the sensitivity of MCF-7 cells to rsTRAIL through suppressing the transcription activity of NF-κB enhancing the

doi: 10.3967/bes2015.112
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processing executioner caspases, which in turn generates executive apoptotic signals[17]. Alternatively, rottlerin prevents TNF-α-dependent NF-κB activation in MCF-7 cells and in HT-29 cells. Taken together, rottlerin can inhibit NF-κB via several pathways in several cell types[18].

Modulation of Wnt/beta-catenin Signaling Wnt/β-catenin signaling regulates the proliferation and differentiation of both normal and malignant cells. In many cancer cells, rottlerin has potent suppressive effect on the signaling of Wnt/β-catenin and mTORC1[9-10]. Since, rottlerin acts as a potent inhibitor for the lipoprotein receptor-related protein-6 (LRP6), an essential Wnt co-receptor for Wnt/β-catenin signaling[9], the reduction of Wnt/β-catenin and mTORC1 signaling pathways, thus rottlerin as an adjuvant may offer a promising approach as novel cancer therapeutic agent.

Autophagy Autophagy is a process of cellular self-eating activated by lysosomal activition due to nutrient depletion. A side of its role in cellular balance maintenance under normal physiological conditions, autophagy is also involved in the development of the genetic diseases and drug resistance in cancer cells[19-21]. The target of rapamycin (TOR) kinase is the major regulator that can inhibit autophagy in the presence of growth factors and abundant nutrients, while AMPK and eIFα control autophagy in case of low energy and nutrient deprivation[22].

Table 1. Rottlerin's Molecular Targets in Cancer

Proposed Mechanism	Targets	Model Used
Inhibition of mTORC1 activity through a novel AMPK and mTORC1 phosphorylation-independent mechanism.	Autophagy[95]	Apoptosis-resistant breast adenocarcinoma MCF-7 cells
Blocking matrix metalloproteinase (MMP)-9 expression.	Metastasis and invasion[32-33]	-
Inhabiting the expression of tissue transglutaminase (TG2), reducing β1 integrin/uPAR/MMP-2 expressions as well as decreasing Src and Eukaryotic elongation factor-2 kinase (eEF-2K) activity.	Cells invasion/migration, self renewing and apoptosis[96-98]	Pancreatic cancer (PaCa)
Cancer cell repopulation is prevented via:		
1. disruption of the cellular signaling caspase 3/7-PKCδ-Akt/p38 MAPK		
2. Inhibition of the markers of angiogenesis (Cox-2, VEGF, VEGFR, and IL-8), and metastasis (MMP-2 and MMP-9), thus blocking production of tumorigenic mediators in tumor microenvironment.		
3. Directly interacting with with proteins of the Bcl-2 of the mitochondria and stimulating cytochrome c release.		
Activation of stress-responsive JNK pathway due to PKCδ inhibition mediates histone H2AX activation.	Apoptosis[14]	Melanoma cell lines
1. Suppressing the two targets of both Wnt/β-catenin and mTORC1 signaling, which are cyclin D1 and and survivin.	Survival pathway[9]	Human prostate cancer PC-3 and DU145 cells and breast cancer MDA-MB-231 and T-47D cells, HEK293 cells
2. Inhibiting Wnt/β-catenin and mTORC1 signaling promoted LRP6 degradation and the low density lipoprotein receptor-related protein-6.		
Reduction of the overexpress p-glycoprotein 1(ABCB1), and thus inhibiting the MDR drug pumping ability.	Drug pumping ability[9]	Multidrug-resistant (MDR) cancer cells MES-SA/Dx5 cells

Rottlerin has been found to mediate autophagy accompanied with apoptosis incidence in many cancer cell types[23]. The potency of rottlerin to induce autophagy and or apoptosis is attributed to its ability to activate several pathways such as AMPK and inhibition of proteasome in a reversible manner[19,23]. In the same context, rottlerin can reversibly inhibit mTORC1 signaling in cells maintained in nutrient-rich conditions leading to autophagy[24]. For instance, rottlerin was mediated early autophagy in breast cancer cells through conversion of LC3-I to LC3-II via proteolytic cleavage, induction of the expression of Atg12 and Beclin-1 and inhibition of Bcl-2, Bcl-xL, XIAP, and cIAP-1 expressions[25].

Rottlerin can work per se as a protein kinase C-delta (PKC-δ) specific inhibitor, and thus could mediate autophagy. It is very important to mention that PKCδ constitutively suppresses autophagy through induction of tissue transglutaminase (TG2)[26]. Rottlerin could also mediate autophagy via a PKC-δ-independent pathway, through loss of mitochondrial membrane potential and translocation of AIF from mitochondria to nucleus[27]. In support of this notion, the knockdown of PKCδ did not block ROT-induced autophagy and cell death, supporting the notion that the effects of ROT are exerted through PKC-δ-independent pathway[12].

Sensitization of Multidrug Resistant Cancer Cells

Multidrug resistance (MDR) is an obstacle in cancer treatment, often associated with decreased intracellular drug accumulation in tumor cells of patient due to enhancement of the drug efflux[28]. P-glycoprotein (P-gp), an ATP-dependent drug efflux pump, is the major player in the development of resistance in cancer cells. Rottlerin, a potent PKCδ inhibitor, was found to reduce P-gp expression and to inhibit the MDR drug pumping ability[29]. Rottlerin sensitized carcinoma cells through augmenting stabilization of TOP1cc, leading to mediate DNA damage stress and, possibly, an impairment of DNA repair capability[13].

Prevention of Cancer Cell Metastasis and Invasion

Metastasis is the major cause of death from cancer[30], initiated by cancer cells migration from the primary tumor to other sites, leading to the forming of secondary tumors. A number of the excellent reports demonstrated that flavonoids are effectively natural inhibitors of cancer invasion and metastasis. Rottlerin's anti-metastasis could promote via dissociating of cell junctions of cancer cells or limiting their migration and invasion activities via PKCδ inhibition[31]. In MCF-7 human breast cancer cells, rottlerin abolishes phorbol 12-myristate 13-acetate (PMA)-induced MMP-9 secretion and cell invasion, as well as ERK/AP-1 activation[32]. Rottlerin blocks matrix metalloproteinase (MMP)-9 expression and thus could prevent invasion in cancer cells[33]. Surprisingly, siRNA knockdown and or even the activation of PKCδ by phorbol esters failed to restore the rottlerin-inhibited migratory ability of CGTH W-2 human follicular thyroid carcinoma cells[34]. Both *in vivo* and *in vitro* and suggest that rottlerin's anti-metastasis activity is attributed to its PKCδ inhibition, thus it can effectively used as a preventive or adjuvant supplement for treatment of cancer[35].

Epigenetic Regulation

In recent years, it has been well documented that epigenetic mechanisms such as DNA methylation and histone modifications regulate many cancer cell activities, and thus emerged as an attractive target for the cancer therapeutics[36]. There are four DNA methyltransferase genes in the human genome, *DNMT1*, *DNMT2*, *DNMT3A*, and *DNMT3B*, which encode proteins with distinct functions[37]. Histone tails and its modifications regulate diverse biological processes including transcription, DNA repair, recombination, cell division, differentiation, etc[38]. Unfortunary, there is no availble information on the epigenetic regulation of rottlerin on cancer cells. In pancreatic β-cells, rottlerin increased histone H4 acetylation, but failed to inhibit HDAC activity, suggesting a potential regulatory effects of rottlerin at the level of increasing the histone acetyltransferase activity[39]. ERK-MAPK inhibitors, particularly rottlerin, promote DNA demethylation via down-regulating DNMT1 expression and other unknown mediator(s) in SW1116 colon cancer cells[40]. Consistent with this argument, in the same cell line (SW1116 cells), rottlerin inhibits cell division and proliferation via regulating DNA methylation and blocking the signaling pathway of mitogen-activated protein kinase (MAPK)[41]. Therefore, there is an urgent need to study epigenetic regulation of rottlerin on different cancer cell lines. The new advantage of epigenetic modifications is that they can be modulated by the treatment with HDAC (histone deacetylase) and DNMT (DNA methyltransferase) inhibitors, and some of which have already been

approved by FDA, like azanucleoside drugs as effective treatments for the treatment of myelodysplastic syndromes and acute myeloid leukemia[42].

BERBAMINE

Berbamine (BBM) is a natural compound derived from the *Berberis amurensis* plant, along with its derivatives, has been shown to exhibit anti-tumor activity against several malignant tissues and cancer cell types[43]. Despite the latter effect, this compound shows a lower cytotoxicity toward normal human cells[44]. BBM displays a strong activity of inducing apoptosis in both estrogen receptor-negative MDA-MB-231 cells and estrogen receptor-alpha-positive MCF-7 breast cancer cells, but not in normal human mammary epithelial cell line MCF10A[45].

As shown in Table 2, BBM induces apoptosis mainly in a wide spectrum of cancer cells and tumors. The underlying mechanisms for BBM's apoptotic activity in cancer cells may involve the down-regulation of bcr/abl gene expression and P210 level[46], the reduction of Bcl-2/Bax protein ratio[47] and the increase in the expression of Fas and P53, which in turn disrupts the mitochondrial membrane and activates caspase-3, -8, and -9[48]. BBM down-regulates the expression of anti-apoptotic protein Bcl-2 and up-regulates the level of pro-apoptotic protein Bax, eventually leading to the reduction of Bcl-2/Bax protein ratio in A549 cells[47]. A novel synthetic BBM derivative, BBMD3, inhibits cell viability and induces apoptosis of cancer stem-like cells via up-regulating JNK-c-Jun/AP-1 signaling pathway and increasing the production of reactive oxygen species (ROS)[49]. Another BBM derivative called bbd24 potently suppressed liver cancer cell proliferation and induced cancer cell death by targeting Ca^{2+}/calmodulin-dependent protein kinase II (CAMKII)[50]. The combined treatment of BBM and gemcitabine could result in the down-regulation of anti-apoptotic proteins (Bcl-2, Bcl-xL) and the up-regulation of pro-apoptotic proteins (Bax, Bid)[51].

Last but not least, BBM suppresses the growth, metastasis and invasion of the highly-metastatic human breast cancer cells via inhibiting Akt and NF-kappaB signaling with their upstream target c-Met and downstream targets Bcl-2/Bax, osteopontin, VEGF, MMP-9, and MMP-2[45].

SPARSTOLONIN B

Sparstolonin B (SsnB) is a novel bioactive compound isolated from *Sparganium stoloniferum*. SsnB inhibits the growth and arrests the cell cycle progression and induces apoptosis in a wide range of neuroblastoma cell lines[52]. The proposed mechanism for its apoptotic effect is attributed to its ability to induce ROS generation, at least in part in neuroblastoma cells with different genetic background[52]. Table 3 shows that SsnB abolishes blood supply for cancer cells and prevents reoxygenation-induced inflammation aside its ability decline the expression of different inflammatory cytokines. SsnB exerts anti-angiogenic property by down-regulating mRNA level of the cell cycle regulatory proteins[53]. Recently, SsnB was suggested as a potent TLR2 and TLR4 antagonist, thus it can attenuate hypoxia-reoxygenation-induced inflammation via inhibiting ERK1/2 and JNK signaling pathways[54].

Table 2. Berbamine's Molecular Targets in Cancer

Proposed Mechanism	Targets	Model Used
Down-regulation of bcr/abl gene expression, reduction of Bcl-2/Bax protein ratio and increase in the expression of Fas and P53, which in turn activates apoptotic pathway via caspase-3, -8, and -9.	The mitochondrial membrane to induce apoptosis[99]	estrogen receptor-negative MDA-MB-231 cells and estrogen receptor-alpha-positive MCF-7 breast cancer cells
Down-regulation of the expression of anti-apoptotic protein Bcl-2 and up-regulation of the level of pro-apoptotic protein Bax.	Apoptosis[47]	A549 cells
Inhibition of Akt and NF-kappaB signaling with their upstream target c-Met and downstream targets Bcl-2/Bax, osteopontin, VEGF, MMP-9, and MMP-2.	Cancer cell growth, migration and invasion[45]	Highly-metastatic human breast cancer cells

In support of this notion, SsnB effectively inhibited inflammatory cytokine expression in mouse macrophages induced by lipopolysaccharide (LPS, a TLR4 ligand), Pam3CSK4 (a TLR1/TLR2 ligand) and Fsl-1 (a TLR2/TLR6 ligand)[55]. It also suppressed LPS-induced cytokine secretion from macrophages and diminished phosphorylation of Erk1/2, p38a, IκBα, and JNK in these cells. In THP-1 cells expressed a chimeric receptor CD4-TLR4, which triggered constitutive NF-κB activation, SsnB effectively blunted the NF-κB activity. SsnB reduced the association of MyD88 with TLR4 and TLR2[56]. Furthermore, SsnB may exert its anti-angiogenic properties in part by downregulating cyclin E2 (CCNE2), cell division cycle 6 (CDC6) and halting their progression through the G1/S checkpoint[53].

SULFORAPHANE

Sulforaphane (SFN) is a natural isothiocyanate that is present in cruciferous vegetables such as broccoli and cabbage. SFN's ability to mediate apoptosis cell cycle arrest is attributed to its ability to activate the cellular death pathways in cancer cells and inactivate protein kinases essential for the cellular proliferation and growth (Table 4). SFN mediates ROS production, which causes apoptosis, DNA damage and mitotic abnormalities in many cancer cell lines[57-58]. SFN may induce apoptosis by death receptor 5, activator protein 1 (AP-1), MAP kinases or mitochondrial dysfunction and suppress concurring prosurvival pathways, e.g. via active inhibition of the nuclear factor-kappa B activation[59-60].

Table 3. Molecular Targets of Sparstolonin B in Cancer

Proposed Mechanism	Targets	Model Used
Down-regulation of mRNA level of the cell cycle regulatory proteins including Cyclin E2 (CCNE2) and Cell division cycle 6 (CDC6), and thus it acts as a potent anti-angiogenic agent.	Angiogenesis[53]	Human umbilical vein endothelial cells (HUVECs) and human coronary artery endothelial cells (HCAECs)
1. Acting as a potent TLR2 and TLR4 antagonist and attenuating hypoxia-reoxygenation-induced inflammation via inhibiting ERK1/2 and JNK signaling pathways.		
2. Preventing the association of MyD88 with TLR4 and TLR2, thus it can serve as a promising lead for the development of selective TLR antagonistic agents for inflammatory	Hypoxia-reoxygenation and inflammation [54-55]	H9c2 cardiomyocyte and macrophages (HEK293T cells and THP-1 cells
3. Inhibiting inflammatory cytokine expression and diminishing phosphorylation of Erk1/2, p38a, IκBα, and JNK in macrophages cell lines.		

Table 4. Sulforaphane's Molecular Targets in Cancer

Model Used	Targets	Proposed Mechanism
Murine and human osteosarcoma cells	Apoptosis[59-60]	Activation of death receptor 5, activator protein 1 (AP-1), MAP kinases or mitochondrial dysfunction and suppress concurring prosurvival pathways, e.g. via active inhibition of the nuclear factor-kappa B activation
-	Cell cycle arrest[58]	Abolishing Chk1 protein kinase and the Cdc25C signaling pathways, thus impairing Cdk1-encoding transcription and promoting G2/M phase arrest.
Leukemia cell lines	Apoptosis[61]	1. Activation of caspases (3, 8, and 9), inactivation of PARP, p53-independent up-regulation of p21(CIP1/WAF1) and inhibition of the Cdc2/Cyclin B1 complex 2. Inhibition of the AKT and mTOR survival pathways
Prostate cancer	Apoptosis[63]	Inactivation of histone deacetylase 6 (HDAC6), and thus enhancing chaperone HSP90 acetylation and causing consequent reduction of androgen receptor (AR) signaling

Additionally, SFN mediated apoptosis in a wide range of leukemic cells through the activation of caspases (3, 8, and 9), the inactivation of PARP, p53-independent up-regulation of p21(CIP1/WAF1) and the inhibition of the Cdc2/Cyclin B1 complex[61].

SFN could also mediate apoptosis via the inactivation of histone deacetylase 6 (HDAC6), which in turn, enhances histone acetylation at the promoters of p21 and Bax[62]. In prostate cancer, SFN inactivates HDAC6 activity, and thus enhances chaperone HSP90 acetylation and cause the consequent reduction of androgen receptor (AR) signaling[63]. SFN also inhibited the AKT and mTOR survival pathways in most of the tested leukemic cells lines[61]. Noteworthy, SFN induced a transcriptome response supportive of G2/M phase arrest, through the inhibition of Chk1 protein kinase and the Cdc25C regulatory pathways, thus it impaired Cdk1-encoding transcription[58].

SFN-inhibits proliferation and mediates cell arrest, since, it can promote the up-regulation of p53 signaling pathway and cause G1/S cell cycle arrest[64]. SFN-treated cells accumulated in metaphase by CDC2 down-regulation and the dissociation of the cyclin B1/CDC2 complex[65]. In human mammary epithelial (MCF-10A) cells, SFN modulates NF-κB and COX-2 overexpression, links inflammation and cancer[66]. SFN is a potent cysteine-reactive inducer which reacts with cysteine sensors of Keap1, a substrate adaptor protein for Cullin3/Rbx1 ubiquitin ligase, leading to the activation of Nrf2[67]. Importantly, the transcription factor NF-E2 p45-related factor 2 (Nrf2) and its negative regulator Kelch-like ECH associated protein 1 (Keap1) control the expression of nearly 500 genes with diverse cytoprotective functions. Queisser and collogues. (2014) studied the capacity of kidney cells to up-regulate transcription factor Nrf2 as a prevention of aldosterone-induced oxidative damage both *in vitro* and *in vivo*[68]. In this study, SFN showed potent activity to prevent aldosterone-induced damage.

PLUMBAGIN

Plumbagin (PLB) is a naturally occurring naphthoquinone isolated from the roots of in *Plumbago zeylanica* L, *Juglans regia*, *J. cinerea*, and *J. nigra*[69]. PLB induces autophagy through the inhibition of PI3K/Akt/mTOR pathway as indicated by reduced phosphorylation of Akt and mTOR[70]. The PLB target is AKT, which plays an important role as anti-apoptotic protein[71]. A recent study suggested that PLB promotes cellular apoptosis and autophagy in tongue squamous cell carcinoma (TSCC) via inhibition of p38 MAPK-and PI3K/Akt/mTOR-mediated pathways with contribution from the GSK3β and ROS-mediated pathways[72]. PLB is also proposed as a potential regulator of cellular growth, metastasis, invasion and apoptosis due to its ability to reduced gene expression of cyclin D1, vascular endothelial growth factor (VEGF)-1, Bcl-xL, survivin, and matrix metalloproteinase-9 (MMP-9), known target products of STAT3 activation in gastric cancinoma[73]. The signaling molecule NF-kB transcription factor plays a major role in the development and progression of various types of cancer[74]. A constitutive and continuous NF-kB activity is observed in various tumors, including lymphoid tumor or myeloid tumor. Therefore, IκB kinase-NF-κB signaling pathway is important for both promoting treatment resistance and preventing host toxicity in cancer chemotherapy[16]. PI3K and Bcl-2 inhibition primes glioblastomac to apoptosis[75]. An increase in proapoptotic genes, e.g. Bad, Bcl-2, p53, NF-Kb, and casp-7 genes, in MCF-7 cells in response to the treatment with PL was noted[76]. Furthermore, PLB has a potent pro-apoptotic and pro-autophagic effect in human non-small cell lung cancer cells, arrests cells in G2/M phase and increases the intracellular level of ROS in both cell lines (A549 and H23 cells)[70]. The treatment of human non-small cell lung cancer cell lines A549, H292 and H460 with PLB increased the intracellular level of ROS, inhibited the activation of NK-κB, NF-κB/p65 nuclear translocation, increased the activity of caspases-3-9, dow-nregulated the expression of Bcl-2 and up-regulated the expression of Bax, Bak, and Cytochrom C[77]. AMPK might be the key mediator of PLB's anti-tumor activity. Since, PLB induces AMPK/Apoptosis signal regulating kinase 1 (ASK1)/TNF receptor-associated factor 2 (TRAF2) association to activate pro-apoptotic c-Jun N-terminal kinases (JNK)-p53 signal axis. Further, after PLB treatment, activated AMPK directly phosphorylates Raptor to inhibit mTOR complex 1 (mTORC1) activation and Bcl-2 expression in colon cancer cells[78]. PLB-caused inhibition of the growth and metastasis of PC-3M cells accompanies inhibition of the expression of: 1) PKCε, pStat3Tyr705, and pStat3Ser727, 2) Stat3 downstream target genes [survivin and Bcl(xL)], 3) proliferative markers Ki-67 and PCNA, 4) metastatic marker MMP9, MMP2, and uPA, and 5) angiogenesis

markers CD31 and VEGF.

Taken together, these results suggest that PLB inhibits tumor growth and metastasis of human PCa PC3-M-luciferase cells, which could be used as a therapeutic agent for the prevention and treatment of human PCa[79]. PLB inhibits breast tumor bone metastasis and osteolysis by modulating the tumor-bone microenvironment and that strongly supports speculation that PLB may serve as a novel agent in the treatment of tumor bone metastasis[80-81]. As shown in Table 5, at the molecular level, PLB abrogated RANKL-induced NF-κB and MAPK pathways by blocking RANK association with TRAF6 in osteoclastogenesis, and by inhibiting the expression of osteoclast-activating factors through the suppression of NF-κB activity[81].

Table 5. Plumbagin's Molecular Targets in Cancer

Proposed Mechanism	Targets	Model Used
1. Inhibition of PI3K/Akt/mTOR pathway through reduction of the phosphorylation of Akt and mTOR 2. Induction of the production of the intracellular ROS, inhibition of the activation of NK-κB, NF-κB/p65 nuclear translocation, increasing the activity of caspases-3-9, down-regulating the expression of Bcl-2 and up-regulating the expression of Bax, Bak, and Cytochrome C.	Autophagy and cell cycle arrest[70,77]	Human non-small cell lung cancer cells
Inhibition of p38 MAPK-and PI3K/Akt/mTOR-mediated pathways with contribution from the GSK3β and ROS-mediated pathways	Autophagy[72]	Tongue squamous cell carcinoma (TSCC)
Reducing gene expression of cyclin D1, vascular endothelial growth factor (VEGF)-1, Bcl-xL, survivin and matrix metalloproteinase-9 (MMP-9), known target products of STAT3 activation	Cellular growth, migration, invasion[73]	Gastric cancinoma
1. Activation of AMPK/Apoptosis signal regulating kinase 1 (ASK1)/TNF receptor-associated factor 2 (TRAF2), association to activate pro-apoptotic c-Jun N-terminal kinases (JNK)-p53 signal axis. 2. Activation of AMPK directly phosphorylates Raptor to inhibit mTOR complex 1 (mTORC1) activation and Bcl-2 expression	Apoptosis[78]	Human colon cancer cells
Inhibition of the growth and metastasis of PC-3M cells accompanies, inhibition of the expression of: 1) PKCε, pStat3Tyr705, and pStat3Ser727, 2) Stat3 downstream target genes [survivin and Bcl(xL)), 3] proliferative markers Ki-67 and PCNA, 4) metastatic marker MMP9, MMP2, and uPA, and 5) angiogenesis markers CD31 and VEGF.	Metastasis of human prostate cancer (PCa) cells[17]	Prostate cancer cell lines (PC-3M cells)
Abrogating RANKL-induced NF-κB and MAPK pathways by blocking RANK association with TRAF6 in osteoclastogenesis, and by inhibiting the expression of osteoclast-activating factors through the suppression of NF-κB activity	Bone metastasis[80-81]	Osteoclast precursor cell
Induction of caspase activation, increasings levels of the Bcl-2 family of proteins and decreasings the level of the anti-apoptotic Bcl-2	Apoptosis[82]	Her2-overexpressing breast cancer

In this context, the anti-proliferative activity of PLB derivatives is associated with apoptosis-mediated cell death, as revealed by caspase activation, increased levels of the Bcl-2 family of proteins and decreased the level of the anti-apoptotic Bcl-2 protein even for Her2-overexpressing breast cancer[82]. PLB inhibits cell growth and induce apoptosis in human GC cells through the NF-κB pathway[83]. The treatment of human melanoma A375 cells with plumbagin resulted in the activation of caspase-3, but not caspase-8. These results suggest that PLB might be useful for TRAIL-based treatment for melanoma[84]. Finally, PLB could promote apoptosis in colonic cancer cells through TNF-α mediated pathway depending on the expression of COX-2 expression[85].

6-SHOGAOL

6-Shogaol is extracted from dietary ginger (*Zingiber officinale*) and a promising anti-cancer agent. Due to its ability to mediate apoptosis in a wide range of cancer cells, 6-shogaol has been widely documented as a potent anti-cancer agent (Table 6). In prostate cancer cells, 6-shogaol shows a potent inhibitory effect on the level of several STAT3 and NF-κB-regulated target genes at the protein level, including cyclin D1, survivin, and cMyc and modulatory effect on mRNA levels of chemokine, cytokine and apoptosis regulatory genes (IL-7, CCL5, BAX, BCL2, p21, and p27)[86]. In pancreatic cancer cells, 6-shogaol inhibits the activation of toll like receptor 4 (TLR4)/NF-κB signaling. 6-Shogaol also suppresses NF-κB signaling and key cell survival regulators e.g. COX-2, cyclinD1, survivin, cIAP-1, XIAP, Bcl-2, and MMP-9, so, it sensitizes pancreatic cancer cells to gemcitabine treatment[87]. Additionally, 6-shogaol can modulate the level of glutathione (GSH) intracellular content and activates p53 pathway that ultimately leads to the release of mitochondria-associated apoptotic molecules such as cytochrome c and cleaved caspases 3 and 9[88].

6-Shogaol can mediate cell arrest through the inhibition of phosphorylation of the signal transducer activator of transcription-3 (STAT3) and decrease the expression of cyclin D1/3, which are target proteins in the Akt signaling pathway[89]. Furthermore, 6-shogaol can inhibit Akt kinase activity, a downstream mediator of EGFR signaling, by binding with an allosteric site of Akt.

On the other hand, the activation of ROS production, caspase pathway activation, tubulin polymerization, AKT/mTOR and matrix metalloproteinase 9 (MMP-9) expressions are proposed as the major underlying mechanisms of 6-shogaol-mediated apoptosis[90]. Additionally, 6-shogaol could mediate apoptosis via dephosphorylation of eIF2α at Ser51 of the N-terminal domain and caspase activation-dependent cleavage of eIF2α[91].

6-Shogaol could also inhibit breast cancer cell invasion by targeting the NF-kB activation cascade, and thus reducing MMP-9 expression[92]. Further investigation into the underlying molecular mechanisms revealed that the levels of key modulators of invadopodium maturation, including

Table 6. 6-Shogaol's Molecular Targets in Cancer

Proposed Mechanism	Targets	Model Used
Inhibition of several STAT3 and NF-κB-regulated target genes at the protein level, including cyclin D1, survivin, cMyc and modulatory effect on mRNA levels of chemokine, cytokine and apoptosis regulatory genes (IL-7, CCL5, BAX, BCL2, p21, and p27)	Apoptosis, survival pathways and cell regulation[86]	Prostate cancer cells
Inhibition of the phosphorylation of signal transducer and activator of transcription-3 (STAT3) and reduction of the expression of cyclin D1/3, which are target proteins in the Akt signaling pathway	Cell arrest and apoptosis[89]	Non-small cell lung cancer cells
Inhibition of cancer cell invasion by targeting the NF-kB activation cascade, and thus reducing MMP-9 expression. Suppression of the levels of key modulators of invadopodium maturation, including c-Src kinase, cortactin and membrane type 1-matrix metalloproteinase (MT1-MMP).	Motility and invasion[93]	Breast cancer cell motility and invasion

c-Src kinase, cortactin and membrane type 1-matrix metalloproteinase (MT1-MMP), were decreased when the cells were treated with 6-shogaol[93].

Finally, one of the major obstacle for chemotherapies in cancer patients is their severe side effects including nausea and emesis. Emetogenic chemotherapy drugs increase serotonin (5-HT) concentration and activate visceral vagal afferent nerve activity. The Use of anti-emetic drugs help to suppress chemotherapy-induced emesis in some patients but not all patients. Unlike well-known competitive 5-HT3 receptor antagonist ondansetron, 6-shogaol acted as non-competitive antagonist, and thus blocked 5-HT-induced emetic signal transmission in vagal afferent neurons[94].

CONCLUSION

Phytochemical-derived compounds from non-edible plants including rottlerin, berbamine, sparstolonin B, sulforaphane, plumbagin and 6-shogaol could provide novel strategies toward designing and synthesizing potent drug molecules specific for many molecular targets in cancer therapy. These compounds could also be combined with the conventional therapies to enhance their potency and prevent tumor recurrence after achieving a successful treatment outcome of cancer patients.

ACKNOWLEDGEMENTS

The author would like to thank Dr. Mohamed Labib Salem, Professor of Immunology, Tanta University, Egypt, for insightful discussions, corrections, keen and sympathetic assistance during revision of the manuscript.

Conflict of Interest: The corresponding author declares no conflict of interest.

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Received: April 12, 2015;

Accepted: November 3, 2015

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